REMARKS

Claim Amendment

Claims 1-4, 8-16, 19 and 20, as amended, are pending in this application for the Examiner's review and consideration. Independent claim 1 has been amended to recite that the microparticles are administered into the walls of the lower esophageal sphincter or the diaphragm. Support for the amendment can be found in the specification, *e.g.*, at page 18, lines 23-30. Thus, no new matter has been introduced by the amendment.

Applicants further submit, as discussed below, that the pending claims are in condition for allowance.

Summary of the Invention and the Argument

The claimed invention is directed to a method of treating gastroesophageal reflux disease ("GERD") by administering a therapeutically effective tissue bulking amount of biocompatible hydrophilic microparticles. The pending claims specifically recite that the administration is into the walls of the lower esophageal sphincter or the diaphragm of a mammal.

The cited references Rajagopalan and Boschetti, whether alone or in combination, do not suggest the claimed invention. Rajagopalan discloses a method of stimulating gastrointestinal ("GI") motility by using ellagic acid. Rajagopalan alleges that ellagic acid has prokinetic activity, and therefore, stimulates motility of the GI tract and is useful in the treatment of GERD. However, there is no disclosure or suggestion in Rajagopalan of a method of treating GERD through tissue bulking, not to mention tissue bulking by administration of biocompatible hydrophilic microparticles into the walls of the lower esophageal sphincter or the diaphragm, as presently claimed. In fact, Rajagopalan is totally silent regarding any method of tissue bulking and only concerns the treatment of GI disorders using a drug, *i.e.*, ellagic acid, that allegedly affects the motility of the GI tract. In other words, Rajagopalan only concerns a method that is clearly distinguished from that of the claimed invention.

Boschetti fails to remedy the deficiencies of Rajagopalan in so far as suggesting the presently claimed invention. Boschetti discloses a microsphere comprising a hydrophilic acrylic copolymer coated with a cell adhesion promoter and a marking agent useful for embolization, *i.e.*, therapeutic vascular occlusion. Boschetti, however, does not disclose or suggest a method for treating GERD by tissue bulking, not to mention tissue bulking through administration of microparticles into the walls of the lower esophageal sphincter or diaphragm, as claimed in the present invention. In fact, Boschetti is silent with regard to treatment of GERD and any method of tissue bulking. As such, Boschetti could not remedy the deficiencies of Rajagopalan, which also lacks disclosure or suggestion regarding any tissue bulking method.

Applicants therefore respectfully submit that the rejection should be reconsidered and withdrawn in view of the claim amendment and argument made herein. A detailed analysis of the shortcomings of the cited references is presented below.

Claim Rejection Under 35 U.S.C. § 103 Should Be Withdrawn

Claims 1-4, 8-16, 19 and 20 have been rejected by the Examiner under 35 U.S.C. § 103(a) as being unpatentable over U.S. Paten No. 5,843,987 to Rajagopalan et al. ("Rajagopalan") in view of U.S. Patent No. 5,635,215 to Boschetti et al. ("Boschetti") for the reasons set forth on pages 3-6 of the Office Action. Applicants respectfully submit that the rejection should be withdrawn in view of the claim amendment and argument made herein.

Rajagopalan discloses a method of stimulating gastrointestinal ("GI") motility with ellagic acid. Rajagopalan alleges that ellagic acid has prokinetic activity, and therefore, stimulates motility of the GI tract and is useful in the treatment of gastroesophageal reflux disease ("GERD") (col. 2, lines 25-34). Rajagopalan alleges that ellagic acid exhibits these effects perorally despite of the fact that it is poorly absorbed from the GI tract (col. 2, lines 34-37).

However, there is no disclosure or suggestion in Rajagopalan of a method of treating GERD through tissue bulking, not to mention tissue bulking by administration of biocompatible hydrophilic microparticles into the walls of the lower esophageal sphincter or

the diaphragm, as presently claimed. In fact, Rajagopalan is totally silent regarding any method of tissue bulking and only concerns the treatment of GI disorders by using a drug, *i.e.*, ellagic acid, that allegedly affects the motility of the GI tract. In other words, Rajagopalan only concerns a method that is clearly distinguished from that of the claimed invention. *See, e.g.*, specification at page 3, lines 7-9.

In contrast, the present invention is directed to a method of treating GERD by using specific tissue bulking materials administered into the muscles surrounding, the GI tract. Specifically, the claimed invention is directed to a method of treating GERD by administering biocompatible hydrophilic microparticles into the walls of the lower esophageal sphincter or the diaphragm, which are muscles surrounding the connection of lower esophagus with the stomach. *See, e.g.*, specification at page 7, lines 26-28, page 18, lines 23-32, and Fig. 1.

The Examiner states that Rajagopalan discloses that pharmaceutical compositions comprising ellagic acid can be made into solid dosage forms such as powders, pills, compressed tablets, hard capsules containing beads or particles of ellagic acid. Office Action at page 3. However, these solid dosage forms are for *oral* administrations (col. 5, lines 31-37). There is no disclosure or suggestion whatsoever in Rajagopalan that the solid dosage forms could be used as implants for tissue bulking or administered into the walls of the lower esophageal sphincter or the diaphragm, as presently claimed. Although Rajagopalan generally discloses that ellagic acid can be formulated into solutions for parenteral administration, there is no indication that the parenteral administration disclosed therein has anything to do with tissue bulking, as presently claimed. In other words, Rajagopalan not only fails to disclose or suggest the claimed invention, it is also totally silent with regard to any tissue bulking materials or methods.

Boschetti fails to remedy the deficiencies of Rajagopalan. Boschetti discloses a microsphere comprising a hydrophilic acrylic copolymer coated with a cell adhesion promoter and a marking agent useful for embolization, *i.e.*, therapeutic vascular occlusion (*See*, col. 1, lines 9-10 and page 15, lines 2-4). The microspheres disclosed in Boschetti are used as emboli in vessels of various processes, including tumors, vascular malformations and

hemorrhagic processes (*See, e.g.*, page 1, lines 9-23). Boschetti, however, does not disclose or suggest a method for treating GERD by tissue bulking, not to mention tissue bulking through administration of microparticles into the lower esophageal sphincter or diaphragm, as claimed in the present invention. In fact, Boschetti is silent with regard to treatment of GERD and any method of tissue bulking. As such, Boschetti could not remedy the deficiencies of Rajagopalan, which also lacks disclosure or suggestion regarding any tissue bulking method.

As the Examiner is well aware, to establish a *prima facie* case of obviousness, three basic criteria must be met. First, there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine the reference teachings. Second, there must be a reasonable expectation of success. Third, the prior art reference (or references when combined) must teach or suggest all the claim limitations. *Manual of Patent Examining Procedure* ("*MPEP*") (Revised 8th Ed., May 2004) § 2143; *In re Fine*, 837 F.2d 1071 (Fed. Cir. 1988); *In re Vaeck*, 947 F.2d 488 (Fed. Cir. 1991); *In re Jones*, 958 F.2d 347 (Fed. Cir. 1992). Applicants respectfully submit that the none of the criteria has been met in this case, and that the Examiner has failed to establish a *prima facie* case of obviousness.

As discussed above, Rajagopalan discloses a method of stimulating gastrointestinal motility with ellagic acid, which is allegedly useful in the treatment of GERD. However, there is no disclosure or suggestion in Rajagopalan of any method of tissue bulking, not to mention the specific method claimed in the present invention. Boschetti, on the other hand, discloses the use of microspheres for embolization, *i.e.*, vascular occlusion, which is in a different field from that of the treatment of GERD, because, as understood by one of ordinary skill in the art, occluding vessels involves different considerations and techniques from using microparticles as a tissue bulking agent in the treatment of GERD.

Applicants respectfully submit that one of ordinary skill in the art at the time of the invention would not have been motivated to modify or combine the teaching of Rajagopalan and Boschetti. Specifically, one of ordinary skill in the art would not have been motivated to combine the disclosure of a GI motility drug, *i.e.*, ellagic acid in Rajagopalan,

with that of microspheres for vascular occlusion, as disclosed in Boschetti, because the references are directed to different fields of treatment, use different materials and approaches.

Applicants further submit that, even if, *arguendo*, the cited references were somehow combined, "the mere fact that references can be combined or modified does not render the resultant combination obvious unless the prior art also suggests the desirability of the combination." *MPEP* § 2143.01 (emphasis original); *In re Mills*, 916 F.2d 680 (Fed. Cir. 1990). Applicants respectfully submit that there was no suggestion of desirability to combine the references at the time of the invention to achieve the presently claimed invention. Therefore, even if the references were indeed combined at the time of the invention, one of ordinary skill in the art would still not be able to achieve the present invention.

Applicants further submit that there was no reasonable expectation of success in combining or modifying the cited references to achieve the present invention. As the Examiner is aware, although obviousness does not require absolute predictability, at least some degree of predictability is required. *MPEP* § 2143.02; *Amgen, Inc. v. Chugai Pharmaceutical Co.*, 927 F.2d 1200, 1207 (Fed. Cir. 1991). In the present case, the microspheres for vascular occlusion as disclosed in Boschetti can hardly be combined with the use of a GI motility drug, as disclosed in Rajagopalan, by one of ordinary skill in the art with any reasonable predictability to achieve the present invention's method of treating GERD by tissue bulking. Specifically, since Boschetti concerns treating a different type of disorders and using a different type of material from that disclosed in Rajagopalan, one of ordinary skill in the art would not expect any reasonable predictability even if they were to combine the disclosures of the references.

In addition, Applicants submit that the combination of Rajagopalan and Boschetti fail to disclose or suggest all the elements of the claimed invention. As discussed, neither reference discloses or suggests any method of tissue bulking, not to mention the specific method of administering biocompatible hydrophilic microparticles into the walls of the lower esophageal sphincter or the diaphragm, as presently claimed.

For the above reasons, Applicants respectfully submit the Examiner has failed to establish a *prima facie* case of obviousness against the claimed invention, and that the cited

references, whether alone or in combinations, fail to obviate the present invention. Therefore, Applicants respectfully request that the rejection under 35 U.S.C. § 103(a) be reconsidered and withdrawn.

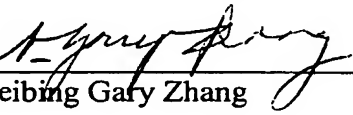
Pending Claims Are In Condition For Allowance

Applicants respectfully submit that, based on the above claim amendment and argument, all pending claims are now in condition for allowance. Should the Examiner not agree, a personal or telephonic interview is hereby requested to resolve any remaining issues and to put the application in condition for allowance.

No fee is believed due for this response, except the required fee for the petition for extension of time submitted herewith. Should any additional fees be required, please charge such fees to Jones Day Deposit Account No. 503013.

Respectfully submitted,

Date: August 20, 2004



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